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Exercise Pathophysiology in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome and Post-Acute Sequelae of SARS-CoV-2

More in Common Than Not?

Phillip Joseph, MD; Inderjit Singh, MD; Rudolf Oliveira, MD, PhD; Christine A. Capone, MD, MPH; Mary P. Mullen, MD, PhD; Dane B. Cook, PhD; Mary Catherine Stovall, BS; Johanna Squires, MSc; Kristine Madsen, MS; Aaron B. Waxman, MD, PhD; and David M. Systrom, MD

TOPIC IMPORTANCE: Postacute sequelae of SARS-CoV-2 (PASC) is a long-term consequence of acute infection from COVID-19. Clinical overlap between PASC and myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) has been observed, with shared symptoms, including intractable fatigue, postexertional malaise, and orthostatic intolerance. The mechanistic underpinnings of such symptoms are poorly understood.

REVIEW FINDINGS: Early studies suggest deconditioning as the primary explanation for exertional intolerance in PASC. Cardiopulmonary exercise testing reveals perturbations related to systemic blood flow and ventilatory control associated with acute exercise intolerance in PASC, which are not typical of simple detraining. Hemodynamic and gas exchange derangements in PASC have substantial overlap with those observed with ME/CFS, suggestive of shared mechanisms.

SUMMARY: This review illustrates exercise pathophysiological commonalities between PASC and ME/CFS that will help guide future diagnostics and treatment. CHEST 2023; ■(■):■-■

KEY WORDS: CPET; hyperventilation; ME/CFS; neurovascular dysregulation; PASC

Since the onset of the COVID-19 global pandemic, > 550 million cases of infection with SARS-CoV-2 have been recorded. A substantial subset of survivors experience

ABBREVIATIONS: AT = anaerobic threshold; iCPET = invasive cardiopulmonary exercise test; ME/CFS = myalgic encephalomyelitis/chronic fatigue syndrome; MIS-C = multi-system inflammatory syndrome in children; niCPET = noninvasive cardiopulmonary exercise test; PASC = postacute sequelae of SARS-CoV-2; PAWP = pulmonary artery wedge pressure; PEM = postexertional malaise; POTS = postural orthostatic tachycardia syndrome; RAP = right atrial pressure; Q_c = cardiac output; V_D/V_T = physiological dead space to tidal volume fraction; V_E = minute ventilation; V_{O_2} = oxygen uptake

AFFILIATIONS: From the Division of Pulmonary, Critical Care, and Sleep Medicine (P. J. and I. S.), Department of Medicine, Yale-New Haven Hospital, Yale University, New Haven, CT; Division of Respiratory Disease (R. O.), Department of Medicine, Federal University of São Paulo (UNIFESP), São Paulo, Brazil; Division of Pediatric Cardiology (C. A. C.) Department of Pediatrics, Cohen Children's Medical Center, Northwell Health, Donald and Barbara Zucker School of Medicine at Hofstra, Manhasset, NY; Department of Cardiology (M. P. M.), Boston Children's Hospital, Harvard Medical School, Boston, MA; Research Service (D. B. C.), William S. Middleton Memorial Veterans Hospital & Department of Kinesiology, University of Wisconsin-Madison, Madison, WI; and the Division of Pulmonary and Critical Care Medicine (M. C. S., J. S., K. M., A. B. W., and D. M. S.), Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA.

CORRESPONDENCE TO: David M. Systrom, MD; email: dsystrom@bwh.harvard.edu

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long-term complications following initial infection, labeled with the all-encompassing term of postacute sequelae of SARS-CoV-2 (PASC) or colloquially referred to as "long COVID." Diagnostic criteria for PASC are not clearly defined, and prevalence estimates range from 20% to 50% of survivors. Afflicted patients are often young and have a history of mild acute disease. Given the new and substantial global burden related to PASC, elucidating mechanisms underlying PASC that inform its diagnosis and treatment is critical.[1]

PASC is recognized as a multisystem syndrome with a broad range of symptoms, including fatigue, chest pain, exertional dyspnea, postexertional malaise (PEM), headache, cognitive impairment or "brain fog," myalgias, and depression.[1] Although the etiology of PASC is unknown, proposed mechanisms include, but are not limited to, autoimmune and hyperinflammatory states following acute infection.[2] Extensive overlap between PASC and myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) has been increasingly recognized.[3] The National Academy of Medicine requires three major criteria for diagnosis of ME/CFS (ie, substantial impairment from fatigue for $>$ 6 months, PEM, and unrefreshing sleep), plus either cognitive impairment or orthostatic intolerance.[4] Given the substantial overlap in symptoms, a common underlying pathophysiology has been suggested.

Noninvasive cardiopulmonary exercise tests (niCPETs), with continuous measurement of pulmonary gas exchange, ventilation, and cardiac monitoring during incremental exercise on a cycle ergometer, offers a diagnostic modality capable of quantifying and explaining the exertional intolerance of PASC and ME/CFS. Up to one-third of patients undergoing CPET after recovery from their acute illness from COVID-19 display a reduction in oxygen uptake (Vo_2).[5,6]

Invasive cardiopulmonary exercise test (iCPET) data suggest that similar exercise pathophysiology underlies both PASC and ME/CFS and argue against deconditioning as the sole explanation for exertional intolerance.[7,8] Such studies suggest that systemic vascular abnormalities, including decreased venous return and peripheral left-to-right shunting, underlie acute exercise intolerance. Combining iCPETs with skin biopsy results showing decreased small neurite density further suggest that dysautonomia underlies vascular dysregulation.[7] Although niCPETs can reveal abnormalities related to aerobic capacity, stroke volume, and ventilatory efficiency,[9] iCPETs elucidate mechanistic underpinnings using direct measurements of pulmonary gas exchange, hemodynamics, oxygen delivery, and utilization.

The aim of the current review was to show the following: (1) niCPET assessment of PASC and ME/CFS; (2) iCPET assessment of PASC and ME/CFS; (3) commonalities underlying both syndromes, including peripheral vascular dysregulation, hyperventilation, and mitochondrial dysfunction; (4) pediatric considerations; and (5) future directions.

Literature Search

Relevant literature was identified via PubMed and was reviewed by the authors for inclusion. The search strategy included the following terms: "myalgic encephalomyelitis/chronic fatigue syndrome," "post-acute sequelae of SARS-CoV-2," "PASC," "cardiopulmonary exercise test," "dyspnea," "post-exertional malaise," "small fiber neuropathy," and "mitochondrial dysfunction." Abstracts were reviewed for relevance. Whenever possible, case series were avoided, and larger, prospective trials and meta-analyses were preferentially used.

Initial Evaluation

Diagnostics performed on the patient at rest, including pulmonary function tests, chest imaging, ECG, orthostatic testing, and echocardiogram, are frequently nondiagnostic in both ME/CFS and PASC. Dyspnea on exertion after COVID-19 has a wide differential diagnosis, such as resolving or persistent interstitial lung abnormalities, pulmonary hypertension, chronic thromboembolic disease/pulmonary hypertension, tracheal stenosis from prior intubation, heart failure, neuromuscular weakness, post-ICU syndrome, and deconditioning.[10] Acute cardiovascular complications related to PASC include myocarditis and pericarditis, with cardiac MRI showing persistent myocardial inflammation months following acute illness.[11] The focus of this review, however, was on patients with ME/CFS and PASC who do not have intrinsic cardiopulmonary abnormalities and present with unexplained exertional intolerance.

Noninvasive CPET

niCPETs are a valuable tool for assessing exercise-related symptoms in ME/CFS and PASC. Patients with ME/CFS experience an elevated perception of effort and have a reduced peak Vo_2 compared with control subjects.[12] Mildly reduced peak Vo_2 has been described

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in ME/CFS with early anaerobic thresholds (ATs) compared with control subjects. Overall, peak V_{O_2} in ME/CFS is believed to be 5.2 to 6.5 mL/kg per minute lower compared with control subjects.[13] Related niCPET findings include inefficient breathing and hyperventilation.[8] Inefficient ventilation is characterized by an increased value of minute ventilation (VE)/V_{CO_2}, which physiologically is related to either hyperventilation or failure to normally decrease physiological dead space to tidal volume fraction (V_D/V_T) during exercise.

Another niCPET variable found in ME/CFS and PASC is chronotropic incompetence. This is of interest given emerging evidence suggesting autonomic dysfunction in patients with ME/CFS.[14] However, chronotropic incompetence has not been reproduced in more recent and larger studies.[13]

Serial niCPETs in ME/CFS 24 h apart assess the ability of patients to recover and replicate physiological performance over time.[15] The rationale for such an approach relies on the fact that patients with ME/CFS experience exercise intolerance along with prolonged recovery from exercise and postexertional aggravation of symptoms, also known as PEM.[4] Two-day niCPET protocols have found that patients with ME/CFS have significantly lower peak V_{O_2}, earlier onset of the AT, and lower work rate parameters on day 2 compared with day 1.[15,16] A meta-analysis identified that: (1) patients with ME/CFS have lower exercise tolerance levels of all parameters on the second CPET compared with control subjects; (2) the difference between patients and control subjects was more pronounced at the AT in relation to peak; and (3) the workload at the AT was different in patients with ME/CFS compared with control subjects.[17]

The biological mechanisms that underlie PEM are not well understood, although CPET has proven useful in terms of mechanistic exploration. Both maximal and submaximal exercise protocols have been used to determine behavioral and physiological consequences of acute exercise challenge. These studies have shown symptom exacerbation of variable intensity, type, and duration,[18] impaired pain regulation,[19] altered immune function markers (eg cytokines, complement levels, natural killer cells),[20] changes in gut microbiome interactions,[21] disruption of metabolites,[22] and altered brain function.[23] Abnormalities in the skeletal muscle exist in patients with ME/CFS related to impaired oxygen delivery during exercise and the inability to recover from exercise-induced pH reductions.[24]

It is clear from these studies that exercise influences multiple physiological systems. However, few studies have directly tested the associations between the physiological and behavioral manifestations of PEM. One recent study reported that neither symptoms nor cardiopulmonary responses to acute exercise were predictive of PEM in veterans with Gulf War illness, a disease that overlaps significantly with ME/CFS.[25] Furthermore, given the overlap between ME/CFS and PASC along with the observation of PEM in PASC,[26] further research into underlying mechanisms is needed.

Invasive CPET

Protocols for iCPET, hemodynamic measurements, and pulmonary gas exchange measurements have been described previously (Fig. 1).[27] Briefly, the pulmonary and radial arteries are catheterized with ultrasound and fluoroscopic guidance, and then a standard right heart catheterization is performed with oxygen saturation measurements to assess for intracardiac left-to-right shunting. Patients then perform a maximum, incremental, upright exercise on a cycle ergometer as ventilation and pulmonary gas exchange are continuously measured. Hemodynamics, including right atrial pressure (RAP), mean pulmonary artery pressure, and mean arterial pressure, are continuously recorded and averaged throughout the respiratory cycle.[28] Pulmonary arterial wedge pressure (PAWP) and arterial and mixed-venous blood gases and pH are measured every minute. RAP and PAWP are measured as the mean of the "a" wave. Cardiac output (Q_c) is calculated by using the direct Fick principle. Predicted peak values for Q_c assume a normal hemoglobin concentration of 14 g/dL, arterial saturation of 100%, and peak mixed venous oxygen saturation of 25%. To correct for anemia, the peak arterial-venous oxygen content difference should approximate the hemoglobin concentration.[29]

Following elimination of pulmonary mechanical limitations to exercise, the iCPET can differentiate central cardiac and peripheral limitations to acute exercise. Central cardiac limitations are due to left-sided heart disease, right-sided heart disease/pulmonary vascular disease, or inadequate cardiac preload, with age-related upper limits of normal defined in the upright position during cycle ergometry vs using flow or cardiac output-corrected pressure slopes (ie, mean pulmonary artery pressure/Q_c or PAWP/Q_c slopes).[30-32] Peripheral limitations, characterized by impaired systemic oxygen extraction, may be due to mitochondrial myopathy or microcirculatory left-to-right shunts (Fig. 2).[29-31,33,34]

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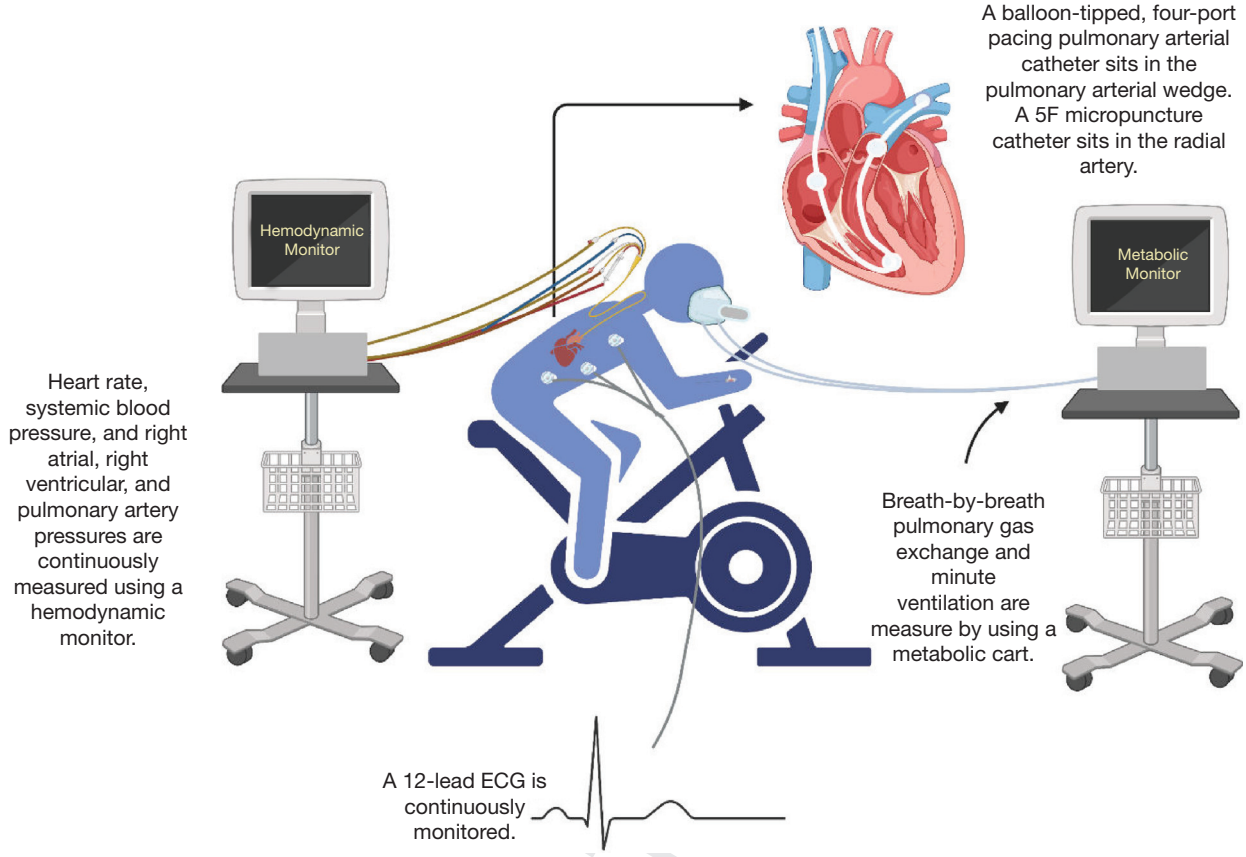

Figure 1 – *Invasive cardiopulmonary exercise test.*

Inadequate Biventricular Preload

The normal central exercise response consists of an increase in Q_c and stroke volume to support the increased demand of skeletal muscle metabolism. Q_c rises as a function of both mechanical mechanisms (ie, skeletal-muscle and respiratory pumps) and neural mechanisms from parasympathetic withdrawal and sympathetic activation. In response, biventricular filling pressures normally increase from splanchnic vasoconstriction and peripheral venoconstriction, resulting in increased blood volume in the central circulation to support the increase in Q_c and stroke volume.[35]

Using iCPETs, systemic vascular dysregulation seems to be similar in ME/CFS and PASC. In a heterogeneous population referred for iCPET investigation of unexplained exertional intolerance, low biventricular filling pressures (ie, "preload failure") explains depressed aerobic capacity in approximately 20% of patients.[34] In studies enriched with PASC[8] and ME/CFS,[7] preload failure seems to be ubiquitous.

The prevalence of small fiber neuropathy (SFN) seems to be high in PASC and ME/CFS. In one small study, SFN was observed in nearly 90% of patients with PASC.[36] One-third of patients with ME/CFS are definitively diagnosed with SFN according to results of protein gene product 9.5-immunolabeled lower-leg epidermal biopsy,[7] a prevalence similar to that observed in fibromyalgia and postural orthostatic tachycardia syndrome (POTS).[37] The prevalence described in ME/CFS may be underestimated due to the use of distal skin biopsies, which may not capture non-length-dependent SFN and are age dependent.[38] Small fibers regulate microvascular tone through sympathetic and parasympathetic cholinergic synapses on perivascular myocytes.[39] SFN and distal axonopathy can reduce venoconstriction, as seen with abnormal lower extremity venous pooling upon standing and low norepinephrine release following sympathetic nervous system stimulation in POTS.[40]

Impaired Systemic Oxygen Extraction

Normally, during intense exercise, sympathetic tone is elevated, but "endogenous sympatholysis" due to local

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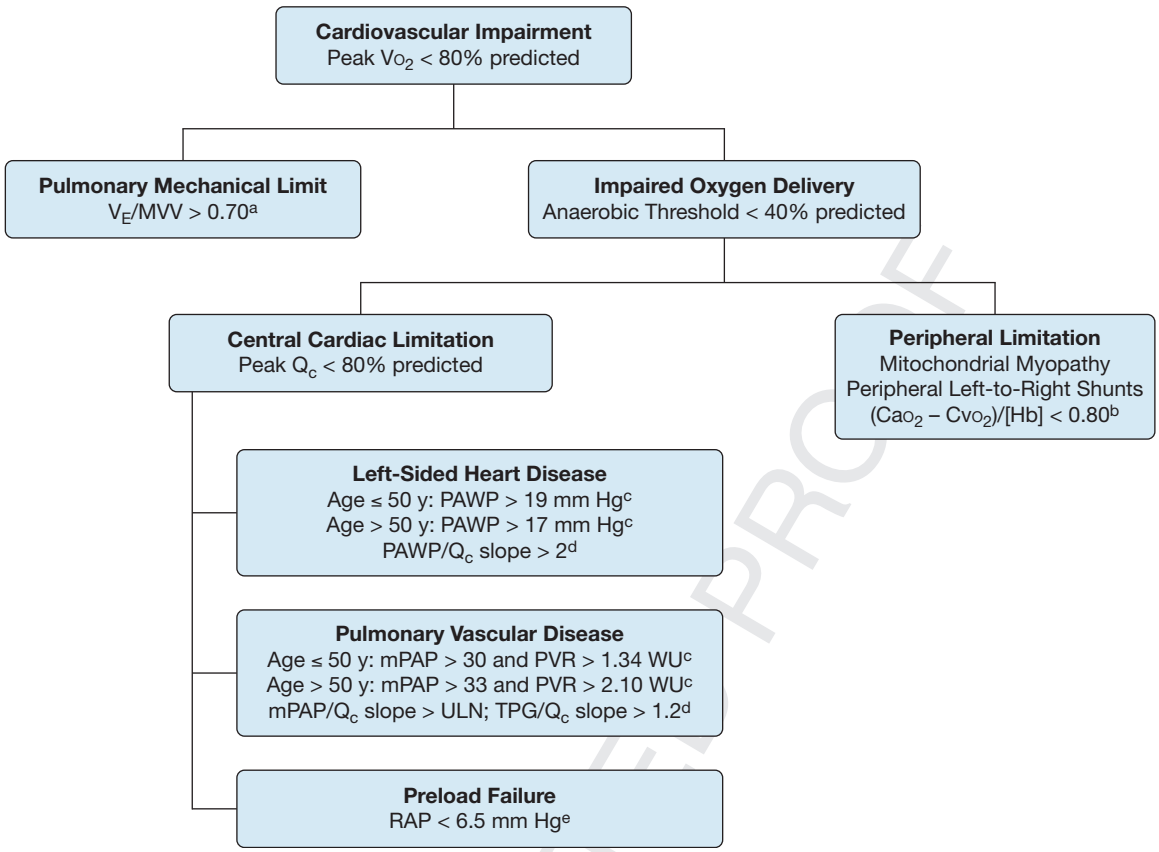

Figure 2 – *Evaluation of undifferentiated exertional intolerance.* [a]*Breathing Reserve Index.*[33] [b]*Peripheral limitation.*[29] [c]*Age-defined upper limits of normal.*[30] [d]*The mPAP/Qc slope is age-dependent whereas the TPG/Qc slope is age-independent.*[31] [d]*Preload failure.*[34] *Cao_2 = arterial oxygen content; Cvo_2 = venous oxygen content; Hb = hemoglobin; mPAP = mean pulmonary artery pressure; MVV = maximum voluntary ventilation; PAWP = pulmonary artery wedge pressure; PVR = pulmonary vascular resistance; RAP = right atrial pressure; Q_c = cardiac output; ULN = upper limit of normal; V_E = minute ventilation; Vo_2 = oxygen uptake.*

vasodilatory substances such as nitric oxide, adenosine, histamine, and prostacyclin decreases systemic vascular resistance and allows for preferential perfusion of the exercising muscle. Acid changes in the muscle capillary right-shift the oxygen-hemoglobin dissociation curve and facilitate oxygen offloading to the muscle capillary.[41]

A high-flow state, suggested by an elevated Q_c/Vo_2 slope throughout incremental exercise and elevated mixed venous oxygen saturation at peak exercise, has been observed in both ME/CFS and PASC.[7,8] Systemic microcirculatory dysfunction may explain this through peripheral left-to-right shunts. Left-to-right shunts may be explained by dysautonomia, which include distal or proximal SFN or a co-existing ganglionopathy, sometimes associated with autoantibodies to the acetylcholine receptor.[42] Results of skin biopsies of patients with SFN and fibromyalgia reveal dysregulated arteriovenous blood flow due to abnormal innervation of arteriovenous shunts, enabling oxygenated blood to bypass capillary beds and return unextracted to the venous circulation.[43] Recent studies have suggested that RBC deformability and endothelial dysfunction may compromise microcirculatory oxygen delivery during exercise.[44,45]

Mitochondrial myopathy has been implicated in both ME/CFS[46] and PASC[47] as an explanation of exertional intolerance and can also present with impaired systemic oxygen extraction during iCPETs. Although Q_c/Vo_2 slopes are elevated in both peripheral left-to-right shunts and mitochondrial dysfunction,[48] the latter's normal peak exercise Q_c can help differentiate the two (Table 1).

Dyspnea on Exertion

Dyspnea on exertion generally results from ventilatory demand that exceeds capacity.[49] In ME/CFS and PASC without intrinsic lung disease, pulmonary mechanics are not limiting. As noted earlier, niCPETs suggest an association between breathlessness and inefficient ventilation (ie, elevated VE/Vco_2), which by the alveolar ventilation equation is due to hyperventilation and/or increased V_D/V_T. The iCPET

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TABLE 1] Differential Diagnosis of Changes in Peak Exercise V_{O_2} and Q_c

	V_{O_2} Peak	Peak Q_c	Diagnosis
Athletic heart	↑	↑	Commensurate increases in V_{O_2} and Q_c at peak exercise is characteristic of endurance trained athletes
Preload failure	↓	↓	Depressed V_{O_2} and Q_c at peak exercise in the absence of a pulmonary mechanical limit suggests preload failure
Left-to-right shunt	↓	↑	Depressed V_{O_2} peak and supranormal Q_c peak is a hallmark of left-to-right shunting
Mitochondrial dysfunction	↓	↔	Depressed V_{O_2} peak and normal Q_c peak suggests mitochondrial dysfunction without cardiac involvement

Q_c = cardiac output; V_{O_2} = oxygen uptake.

allows direct measurements of both, with radial arterial blood gases allowing minute-to-minute assessment of acid-base status and mixed expired CO_2 from the metabolic cart, with calculation of V_D/V_T by using the Bohr equation.

In patients with PASC and ME/CFS without intrinsic cardiopulmonary disease, ventilatory inefficiency and an erratic breathing pattern[50] are frequently observed and associated with dyspnea. Interestingly, the aberrant increase in VE/VCO_2 is entirely due to hyperventilation and not due to the failure of the V_D/V_T to fall normally.[8,51] This is in contradistinction to heart failure[52] and pulmonary arterial hypertension,[53] in which ventilatory inefficiency is driven by both elevated V_D/V_T and hyperventilation. In patients with heart failure, skeletal muscle group III/IV afferents play an important role in the exaggerated hyperventilatory response seen during exercise.[52] These metaboreceptors detect byproducts of muscle metabolism and stimulate group III/IV afferents of the spinal cord to the medullary respiratory centers to stimulate ventilation.[53] It is possible that in PASC and ME/CFS, similar to patients with heart failure, an exaggerated skeletal muscle metaboreflex drives hyperventilation. This heightened ventilatory response is associated with exertional dyspnea. Respiratory alkalemia causes a leftward shift of the oxygen dissociation curve, increasing hemoglobin-oxygen affinity and inhibiting systemic capillary oxygen offloading, contributing to the reduction in peak exercise V_{O_2}.[41,51]

Deconditioning

Deconditioning has been implicated as an explanation for exertional intolerance in ME/CFS and PASC.[5,6] iCPETs offer objective evidence arguing against simple deconditioning as an explanation for these symptoms. Low peak exercise Q_c and higher intracardiac filling pressures are observed in detrained individuals due to cardiac atrophy and decreased ventricular compliance,[54,55] diametrically opposed to the previously discussed preload failure hemodynamic phenotype. In a similar fashion, peripheral oxygen extraction is little affected by deconditioning.[54]

Hypovolemia has been offered as an explanation for low intracardiac filling pressures in POTS, ME/CFS, and PASC. The lack of NPO status for iCPETs, absence of diuretic and venodilator drugs, and increased peak exercise RAP, Q_c, and V_{O_2} in a recent randomized, placebo-controlled iCPET study of pyridostigmine in ME/CFS suggest that neurovascular dysregulation underlies preload failure, rather than hypovolemia.[7,8,56]

Special Consideration in Pediatrics

Children with SARS-Cov2 often have asymptomatic or mild disease. However, a minority of pediatric patients

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have a more severe course, either acutely manifesting as ARDS and/or myocarditis or 4 to 6 weeks later as a postinflammatory disorder known as multi-system inflammatory syndrome in children (MIS-C). For those with MIS-C, illness is severe, with approximately 80% of patients requiring intensive care, approximately 50% exhibiting features of left ventricular systolic dysfunction and myocarditis, 10% to 20% developing acute coronary artery aneurysms, 20% with ECG abnormalities/arrythmias, and 4% requiring extracorporeal membrane oxygenation.[57,58]

Although many surviving patients return to their baseline health within 8 weeks of their illness, a proportion of children experience chronic health impairments.[59] Meta-analyses of observational studies including > 80,000 children report long COVID symptoms in 25% of children following SARS-CoV2 infection.[60] Prominent symptoms include exercise intolerance, shortness of breath, and orthostatic intolerance. Such impairments may be secondary to the severity of illness, post-ICU syndrome, critical illness myopathy, residual cardiac dysfunction, or deconditioning. However, these symptoms also occur in outpatients with mild SARS-CoV2 illness, which would be more suggestive of a pathophysiology similar to ME/CFS. Fatigue and PEM are among the most common symptoms reported in children with long COVID. A recent prospective, multicenter study identified persistent symptoms and activity intolerance at 2 to 4 months following hospitalization for 26.9% of children hospitalized with acute COVID-19 and 30% of those hospitalized with MIS-C.[61] Meta-analysis also showed that these symptoms were among the most commonly reported in children who were not hospitalized.[60] PASC symptoms in children may be independent of the severity of the initial infection and occur despite resolution of laboratory and echocardiographic abnormalities.[61,62]

There are limited data regarding formal exercise testing in patients with PASC or MIS-C. In a group of 40 children followed up after hospitalization for MIS-C, 45% had 6-min walk test performances below the third percentile for their age and sex at 6 months' postdischarge.[63] In addition, abnormal cardiorespiratory responses during exercise were shown in a small number of patients after hospitalization for MIS-C. In this sample, all patients had lower peak V_{O_2}, impaired oxidative metabolism (lower VO_{2VAT} and OUES), and ventilatory inefficiency (higher V_E/VCO_2) compared with normal values for the cohort.[64]

Although possibly connected to residual cardiac disease, both impaired 6-min walk test performance and low peak V_{O_2} occurred in some patients who had normal inflammatory markers and normal ventricular systolic function on echocardiogram. It is unclear whether the persistent symptoms of PASC in children may have some contribution from deconditioning, as suggested from these healthy control studies, or are entirely from the pathobiology of the illness itself.[65]

Shortness of breath has also been reported as a frequent symptom in children with long COVID. A single-center study comparing pulmonary function testing in 73 children and adolescents following SARS-CoV-2 seroconversion showed lack of impairment except in those with severe infection and no difference in follow-up pulmonary function testing compared with a group of healthy control subjects.[66] The mechanisms underlying the discrepancy between subjective persistent respiratory report of symptoms and normal pulmonary function in children with long COVID are unclear, but this finding is similar to what has been reported in ME/CFS.

Orthostatic intolerance, described in most patients with ME/CSF, is a common finding in adolescents with PASC with reported orthostatic symptoms as well as descriptions of palpitations, dizziness, and lightheadedness.[59,62] In some instances following COVID-19 infection, adolescents may be diagnosed with POTS in the setting of excessive heart rate increase without hypotension while upright or other forms of dysautonomia, reinforcing the importance of orthostatic testing in the evaluation of PASC symptoms in young patients.[59]

In addition to obtaining a careful history of SARS-CoV-2 illness, complications, and comorbidities, testing in children and adolescents with PASC (severe illness as well as mild) should include laboratory analysis, echocardiogram with and without cardiac MRI, pulmonary function tests, 6-min walk test, CPET, and orthostatic testing. Ongoing large prospective multicenter trials such as the National Institutes of Health-sponsored Long-term Outcomes after the Multisystem Inflammatory Syndrome in Children (MUSIC) study and the National Institutes of Health Researching COVID to Enhance Recovery (RECOVER) program, studying post-acute sequelae of COVID-19, will be crucial to our understanding of this disease, allowing for more definitive clinical guidelines for management and treatment of children with PASC.

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Knowledge Gaps and Future Directions

Given the significant global burden of ME/CFS and the suspected societal costs of PASC, further research into underlying mechanisms and treatment is needed. iCPETs offer insights into the underlying pathophysiology of ME/CFS and PASC that cannot be derived from testing of the patient in the resting state or noninvasively. Future directions using niCPETs in conjunction with plasma -omic signatures may be useful. Metabolomics reveal exercise perturbations in lipid- and energy-related pathways, with commonality observed with glutamate metabolism.[22] Metabolic profiles of PASC show elevated ferritin, D-dimer, erythrocyte sedimentation rate, and C-reactive protein, suggestive of a chronic inflammatory state.[67] Targeting these pathways may offer benefit related to symptom burden.

There are no US Food and Drug Administration-approved treatments for ME/CFS and PASC. Nonpharmacological therapies can be offered, although the data are based on treating patients with POTS. These include increased dietary salt and fluid intake, activity modification such as leg crossing and squatting, and the use of compression stockings and abdominal binders.[68] Although graded exercise has been recommended for POTS, PEM makes exercise recommendations difficult in ME/CFS and PASC, supporting the role of CPET-guided exercise prescriptions in rehabilitation efforts. Prior studies have evaluated cognitive behavioral therapy, graded exercise,[69] IV immunoglobulin,[70] and B-cell depletion.[71] Robust evidence exists for treating autoantibody-mediated disease such as myasthenia gravis; however, limited data support the use of immunosuppression in autoantibody-associated ME/CFS.[72] Increasing recognition of mitochondrial dysfunction underlying PASC has led to clinical trials evaluating compounds to improve muscle metabolism.[73] However, limited efficacy and data exist for the use of mitochondrial supplements such as ubiquinol, alpha-lipoic acid, L-carnitine, oxaloacetate, and B vitamins, although little harm results from their use.[74,75] Finally, a double-blind, randomized, placebo-controlled trial of a single dose of pyridostigmine in patients with ME/CFS undergoing iCPETs showed improvement in V_{O_2} by increasing Q_c and right ventricular filling pressures.[56] Long-term, placebo-controlled studies are needed to assess for improvements in PEM and exercise tolerance.

Conclusions

PASC and ME/CFS overlap in both symptom burden and exercise derangements. niCPETs are useful in characterizing aerobic capacity and evaluating ventilatory inefficiency, the latter caused by hyperventilation. Two-day niCPET protocols may provide a diagnostic tool by showing a decrement in peak V_{O_2} on day 2, potentially due to PEM. Neurovascular dysregulation observed with iCPETs further explains exercise intolerance in PASC and ME/CFS through impaired cardiac preload and peripheral oxygen extraction, associated with autonomic dysfunction, SFN, ganglionopathy, and mitochondrial dysfunction. Future studies targeting these pathways are needed to reduce the substantial global burden of PASC and ME/CFS.

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